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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/661,927	09/14/2000	William J. Dower	019282-000110US	1158

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EXAMINER
EPPERSON, JON D

ART UNIT	PAPER NUMBER
1639	

DATE MAILED: 12/01/2004

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	09/661,927	DOWER ET AL.	
	Examiner	Art Unit	
	Jon D Epperson	1639	

-- The MAILING DATE of this communication appears on th cover sheet with the correspond nce address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *23 August 2004*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1 and 3-77* is/are pending in the application.

4a) Of the above claim(s) *4-13,17-24,36,38,39,41-45,51,55,57,59-65, 67 and 69-77* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1,3,14-16,25-35,37,40,46-50,52,53,56,58,66 and 68* is/are rejected.

7)☒ Claim(s) *54* is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date *8/23/04*.
4) ☒ Interview Summary (PTO-413) Paper No(s)/Mail Date. *7/13/04* .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

DETAILED ACTION

Request for Continued Examination (RCE)

1. A request for continued examination (RCE) under 37 CFR 1.114, including the fee set forth in 37 CFR 1.17(e), was filed in this application after final rejection. Since this application is eligible for continued examination under 37 CFR 1.114, and the fee set forth in 37 CFR 1.17(e) has been timely paid, the finality of the previous Office action has been withdrawn pursuant to 37 CFR 1.114. Applicant's submission filed on 8/23/04 has been entered. Claims 1-77 were pending. Applicants canceled claim 2 and amended claims 1, 25-28, 48 and 68. Therefore, claims 1 and 3-77 are currently pending. Claims 4-13, 17-24, 36, 38-39, 41-45, 51, 55, 57, 59-65, 67 and 69-77 are drawn to non-elected species and/or inventions and thus these claims remain withdrawn from further consideration by the examiner, 37 CFR 1.142(b), there being no allowable generic claim. Therefore, claims 1, 3, 14-16, 25-35, 37, 40, 46-50, 52-54, 56, 58, 66 and 68 are examined on the merits in this action. An action on the merit follows.

Those sections of Title 35, US code, not included in the instant action can be found in previous office actions.

Withdrawn Objections/Rejections

2. All rejections are withdrawn in view of Applicants' arguments and/or amendments.

New Rejections

Claims Rejections - 35 U.S.C. 102

The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless -
>
> (b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

3. Claims 1, 49, 50, 52, 53, 56, 58, 66 and 68 are rejected under 35 U.S.C. 102(b) as being anticipated by Boyer et al. (Boyer, J. L.; Ananthanarayanan, O. -C.; Hofmann, A. F.; Schteingart, C. D.; Hagenbuch, B.; Stieger, B.; and Meier, P. J. "Expression and characterization of a functional rat liver Na^+ bile acid cotransport system in Cos-7 cells" *American Journal of Physiology* **1994**, *266(3)*, G382-G387).

For ***claims 1, 49, 50, 52 and 53***, Boyer et al. (see entire document) disclose screening a functional rat liver Na^+ bile acid cotransport system in Cos-7 cells with a library of fluorescent-conjugated labeled bile acids (e.g., see abstract, "... the transiently transfected COS cells were screened with fluorescent-conjugated labeled bile acids for evidence of expression of the cotransporter"), which anticipates claim 1. For example, Boyer et al. disclose **(a)** providing a library comprising different complexes, each complex comprising a compound and a reporter, the compound varying between different complexes (e.g., see Table 1 wherein Cholyl-Glycyl Fluorescein and Chenodeoxycholyl-Lysyl-NBD are disclosed; in this scenario the "different" compounds are the Cholyl and Chenodeoxycholyl portions and both contain either a Fluorescein or NBD reporter).

Boyer et al. also disclose **(b)** providing a population of cells, one or more of which expresses one or more carrier-type transport proteins (e.g., see title wherein COS-7 cells that express the rat liver Na^+ bile acid cotransporter are disclosed; see also page G384, column 2, first paragraph; see also G386, column 2, first full paragraph). Boyer et al. also disclose **(c)** contacting the population of cells with a plurality of complexes from the library (e.g., see Table 1 wherein the measured uptake values are disclosed). Boyer et al. also disclose **(d)** detecting a signal from the reporter of a complex while internalized within a cell (e.g., see figure 2 wherein fluorescent-labeled bile acids are detected in COS-7 cells while said bile acids are internalized). The requirement that the reporter "preferentially generate the signal once the reporter is internalized within the cell" has not been given any patentable weight because the use of the term "preferential" has broadly been interpreted to be an "optional" method step that is ultimately determined by the investigator (i.e., it is "preferential" to the investigator or "not required"). Finally, Boyer et al. disclose that the detected signal provides an "indication" that a complex whose reporter generated the signal comprises a compound that is a substrate for a carrier-type transport protein (e.g., see Table 1; see also pages G383-G384, especially page G384, column 2, paragraph 1, "These findings [referring to the fluorescent signal detection studies] indicate ... the transfected COSS-7 cells expressed ... bile acid transport protein to facilitate specific uptake of these two fluorescent bile acid analogues and that COS-7 cells transfected without the cDNA clone do not contain functional bile cid transport carriers").

For ***claim 56 and 58***, Boyer et al. disclose the "Glycyl" or "Lysyl" linkers or, in the alternative, a "covalent bond" links the compound to the reporter, which is a stable linker lacking a cleavage site.

For ***claim 66***, Boyer et al. disclose Cholyl and Chenodeoxycholyl, which represent small molecules.

For ***claim 68***, Boyer et al. teach the use of controlled cells (e.g., see Boyer et al., figure 1 wherein cells with and without the "insert" are described; see also page G384, column 2, paragraph 1).

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

4. This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(e), (f) or (g) prior art under 35 U.S.C. 103(a).

5. Claims 1, 3, 14-16, 25-35, 37, 40, 46-50, 52, 53, 56, 58, 66 and 68 are rejected under 35 U.S.C. 103(a) as being unpatentable over Boyer et al. (Boyer, J. L.; Ananthanarayanan, O. -C.; Hofmann, A. F.; Schteingart, C. D.; Hagenbuch, B.; Stieger, B.; and Meier, P. J. "Expression and characterization of a functional rat liver Na^+ bile acid cotransport system in Cos-7 cells" *American Journal of Physiology* **1994**, *266(3)*, G382-G387) and Schaeffer et al. (Schaeffer, J. M.; Hsueh, A. J. W. "α-Bungarotoxin-Luciferin As a Bioluminescent Probe for Characterization of Acetylcholine Receptors in the Central Nervous System" J. Biol. Chem. 1984, 259(4), 2055-2058) and Thompson et al. (US Pat. No. 5,824,485) (Date of Patent is **October 20, 1998**).

For ***claims 1, 49, 50, 52, 53, 56, 58, 66 and 68***, Boyer et al. teach all the limitations stated in the 35 U.S.C. 102(b) rejection above (incorporated in its entirety herein by reference), which anticipates and, consequently, also renders obvious claims 1, 49, 50, 52, 53, 56, 58, 66 and 68.

For ***claim 26***, Boyer et al. teach the use of controlled cells (e.g., see Boyer et al., figure 1 wherein cells with and without the "insert" are described).

For ***claim 37***, Boyer et al. disclose the use of different reporters including fluorescent labels (e.g., see Table I, wherein Fluorescein and NBD are disclosed).

For ***claim 47***, Boyer et al. disclose a population of cells that have been transformed with a DNA library encoding the one or more transport proteins (e.g., see figure 1 showing DNA "insert" for transporter).

The prior art teaching of Boyer et al. differ from the claimed invention as follows:

For ***claim 3***, Boyer et al. fail to teach a reporter with a cleavable site.

For ***claims 14-16***, Boyer et al. fail to teach a reporter comprising a substrate for an enzyme wherein the enzyme.

For ***claims 25, 27 and 35***, Boyer et al. fail to teach contacting a plurality of different complexes with different cells in a single reaction vessel or different cells in separate reaction vessels.

For ***claims 28-34, 40***, Boyer et al. fail to teach cells with different characteristics e.g., morphology, etc.

For ***claim 46***, Boyer et al. fail to teach the use of a "focused" library.

For ***claim 48***, Boyer et al. fail to teach the "isolation" of unknown transporter compounds. The transporter in Boyer et al. was known and thus did not need to be isolated.

However, the combined references of Schaeffer et al. and Thompson et al. teach the following limitations that are deficient in Boyer et al.:

For ***claim 3, 14-16***, the combined references of Schaeffer et al. and Thompson et al. (see entire documents) teach the use of luciferin conjugates, which are substrates for the enzyme luciferase, within a cell to produce upon enzymatic cleavage a detectable signal (e.g., see Schaeffer et al., abstract; see also Thompson et al., column 22, line 25; see also column 36, line 23). Please note that these reporters would "preferentially" generate a signal after being internalized within the cell.

For ***claims 25, 27 and 35***, the combined references of Schaeffer et al. and Thompson et al. teach different screening formats with populations of different cells in

single and/or different containers (see column 34, line 32; see also column 28, line 57; see generally section 5.2).

For ***claims 28-34, 40***, the combined references of Schaeffer et al. and Thompson et al. teach different characteristics including different stains, epitopes, etc. (see section 5.2.3; see column 30, line 50; see also column 29, line 51; see also column 10, paragraph 2; see also column 10, last paragraph; column 38, line 64; column 32, line 63).

For ***claim 46***, the combined references of Schaeffer et al. and Thompson et al. teach the use of a focused library (e.g., see column 32, lines 15-16; see section 5.2.3).

For ***claim 48***, the combined references of Schaeffer et al. and Thompson et al. disclose the "isolation" of unknown expression products using HTS techniques (e.g., column 5, lines 64-65).

It would have been obvious to one skilled in the art at the time the invention was made to use the screening method as taught by Boyer et al. with the luciferin conjugates as taught by the combined teachings of Schaeffer et al. and Thompson et al. because Schaefer et al. state that the conjugates can be applied generally to a wide range of systems (e.g., see Schaefer et al., paragraph bridging pages 2057-2058, "future conjugations of luciferin to various other ligands will provide the basis for the development of sensitive bioluminescent immunoassays and bioluminescent ligand receptor assays"), which would encompass the transporter protein ligands disclosed by Boyer. Furthermore, one of ordinary skill in the art would have been motivated to use the luciferin conjugates because of their high sensitivity (e.g., see Schaeffer et al., abstract) and because luciferin is stable to proteolytic enzymes that might be found within the cell

and is also small (e.g., see Schaeffer et al., page 2057, column 2, paragraph 1). In addition, one of ordinary skill in the art would have been motivated to use the methods of Thompson et al. because they could be used to screen for transporters on cells that do not grow very well (e.g., see Thompson et al, column 12, lines 55-57), which would increase the variety of transporters that could be screened. Finally, a person of skill in the art would have reasonably been expected to be successful because Schaeffer et al. explicitly states that the luciferin conjugates can be generally applied to a wide range of systems (see above) and Thompson et al. demonstrates that luciferin/luciferase reporter systems can be successfully applied to high throughput cell based assays (e.g., see Thompson et al., column 22, line 25; see also column 36, line 23).

Allowable Subject Matter

6. No claims are allowed. However, claim 54 would be allowable if rewritten in independent form including all of the limitations of the base claim and any intervening claims to overcome the objections to being dependent upon a rejected base claim.

Conclusion

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Jon D Epperson whose telephone number is (571) 272-0808. The examiner can normally be reached Monday-Friday from 9:00 to 5:30.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Andrew Wang can be reached on (571) 272-0811. The fax phone number for the organization where this application or proceeding is assigned is (703) 872-9306.

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the receptionist whose telephone number is (571) 272-1600.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished

applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

Jon D. Epperson, Ph.D.
November 21, 2004

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